Remarks

Applicants thank the Examiner and his supervisor for discussing the rejections and the claims during the interview on April 26, 2007. Applicants are submitting comparative data in view of the helpful comments provided by the Examiner and his supervisor during this discussion.

Objection to the Specification

In the Office Action mailed on February 7, 2007, the Examiner pointed out an obvious typographical error on page 3, line 1 of the specification. In the attached amendment, Applicants have corrected this typographical error, by replacing the term "associate" with "dissociate". No new matter has been added by way of this amendment, entry of which is respectfully requested.

Amendment to Claim 33

Claim 33 as amended further clarifies the claimed method, by specifying that the microparticles release monomeric or dimeric insulin upon dissociation. Support for this amendment can be found in the specification at least at page 2, line 29 until page 3, line 2 and page 16, lines 16-19.

Rejections Under 35 U.S.C. § 102

Claims 33 and 36 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,352,461 to Feldstein *et al.* ("Feldstein"). Claims 33, 35, 37, and 38 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,503,852 to Steiner *et al.* ("Steiner"). Applicants respectfully traverse these rejections.

The claimed methods

Independent claim 33 defines a method for delivering monomeric or dimeric insulin to a patient in need thereof. The method includes administering to the patient a delivery formulation for the monomeric or dimeric insulin comprising an effective amount of insulin complexed with a diketopiperazine derivative. The delivery formulation is prepared by complexing the insulin with microparticles of the diketopiperazine derivative. The diketopiperazine derivative has the formula, 2,5-diketo3,6-di(4-X-aminobutyl)piperazine, where X is fumaryl, succinyl, maleyl, or glutaryl. Claim 33, as amended, also specifies that the micropaticles release monomeric or dimeric insulin upon dissociation.

a. U.S. Patent No. 5,352,461 to Feldstein et al. ("Feldstein")

Feldstein describes a drug delivery system based on the formation of diketopiperazine microparticles by co-precipitation due to a change in pH. Feldstein discloses encapsulating drug within microparticles "by dissolving the diketopiperazine in bicarbonate or other basic solution, adding the drug in solution or suspension to be encapsulated, then solidifying the structure by adding acid." (Feldstein, col. 5, lines 39-43)

The Examiner acknowledges that Feldstein does not disclose complexing insulin with microparticles of a diketopiperazine derivative (*see* Office Action mailed February 7, 2007, page 3). The Examiner requested comparative data in support of Applicants' assertion that when

insulin is encapsulated in a diketopiperazine, it is not inherently complexed with the diketopiperizine. (*Id.*)

As shown by the attached Declaration under 37 C.F.R. §1.132 by Marshall Grant, the methods disclosed in Feldstein produce encapsulated particles, which are not inherently complexed. The Declaration compares particles produced using two co-precipitation experiments, as described in Feldstein, with the particles produced when insulin was adsorbed onto a preformed fumaryl-diketopiperizine ("FDKP") particle, as described in the pending application. The results demonstrate that the co-precipitation-based encapsulation methods described in Feldstein can produce microparticles with different properties than those produced using a complexation method, as required by the pending claims. As shown by the experiments described in the Declaration, the insulin in the microparticles produced by the complexation method was more stable than in microparticles produced using the methods disclosed in Feldstein. Thus the disclosure of the co-precipitation-based encapsulation methods of Feldstein does not inherently disclose complexation.

Feldstein does not disclose complexing insulin to microparticles of the diketopiperazine derivative nor delivery of monomeric or dimeric insulin. Accordingly, independent claim 33 and dependent claim 36 are novel over Feldstein.

b. U.S. Patent No. 5,503,852 to Steiner et al. ("Steiner")

Like Feldstein discussed above, Steiner also describes encapsulating an active agent in diketopiperazine microparticles, using co-precipitation to capture the agent within the diketopiperazine precipitate (col. 9, line 55 to col. 10, lines 8).

The Examiner acknowledges that Steiner does not disclose complexing insulin with microparticles of a diketopiperazine derivative (*see* Office Action mailed February 7, 2007, page 4). The Examiner requested comparative data in support of Applicants' assertion that when insulin is encapsulated in a diketopiperazine, it is not inherently complexed with the diketopiperizine. (*Id.*)

As shown by the attached Declaration under 37 C.F.R. §1.132 by Marshall Grant, the methods disclosed in Steiner produce encapsulated particles, which are not inherently complexed. The Declaration compares particles produced using two co-precipitation experiments, as described in Steiner, with the particles produced when insulin was adsorbed onto a preformed fumaryl-diketopiperizine ("FDKP") particle, as described in the pending application. The results demonstrate that the co-precipitation-based encapsulation methods described in Steiner can produce microparticles with different properties than those produced using a complexation method, as required by the pending claims. As shown by the experiments described in the Declaration, the insulin in the microparticles produced by the complexation method was more stable than in microparticles produced using the methods disclosed in Steiner.

Thus the disclosure of the co-precipitation-based encapsulation methods of Steiner does not inherently disclose complexation.

Steiner does not disclose complexing insulin to microparticles of the diketopiperazine derivative nor delivery of monomeric or dimeric insulin, as required by claim 33. Accordingly, independent claim 33, and dependent claims 35, 37, and 38 are novel over Steiner.

Rejections Under 35 U.S.C. § 103

Claims 33 and 35-39 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,976,569 to Milstein ("Milstein"). Claims 40-42 were rejected under 35 U.S.C. § 103(a) as obvious over Milstein in view of the Abstract of Edelman, S.V. "Type II Diabetes Mellitus," Advances in Internal Medicine, 1998, pp 449-500) ("Edelman"). Applicants respectfully traverse these rejections.

a. U.S. Patent No. 5,976,569 to Milstein ("Milstein")

Milstein describes a composition comprising an active agent and at least one mono-N-substituted, di-N-substituted, or unsubstituted diketopiperazine carrier (col. 2, lines 29-32). The compositions are in the form of microspheres (col. 6, lines 65-66).

Example 25 discloses a method for encapsulating calcitonin in diketopiperazine. The method requires the co-precipitation of calcitonin and the diketopiperazine to form the microparticles. In the Office Action mailed on May 17, 2006, the Examiner referenced Examples 26 and 26A, which provide *in vivo* tests of these particles in fasted rats.

Like Feldstein and Steiner, discussed above, Milstein does not disclose complexing insulin to microparticles of a diketopiperazine derivative nor delivery of monomeric or dimeric insulin, as required by claim 33. As shown by the data in the attached Declaration, the co-precipitation-based encapsulation methods can produce microparticles with different properties than those produced using a complexation method, as required by the pending claims.

Further, Milstein contains no suggestion to modify its methods to prepare delivery formulations by complexing the insulin with microparticles of the diketopiperazine derivative, as required by claim 33. As shown by the attached Declaration, one cannot simply extrapolate from the co-precipitation-based encapsulation method disclosed in the prior art to derive a method that results in complexation between the insulin and the diketopiperazine derivative. Accordingly, independent claim 33 and dependent claims 35-39 are not obvious over Milstein.

b. Edelman

Edelman describes the use of combination therapy (bedtime intermediate-acting insulin in combination with daytime oral antidiabetic agents) for the treatment of Type II diabetes. Edelman states that if the combination therapy is not successful, a split-mixed regimen using premixed 70/30 insulin pre-breakfast and pre-dinner can be used. Edelman contains no discussion or suggestion of diketopiperazine microparticles, let alone complexing insulin with microparticles of a diketopiperazine derivative.

c. The combination of Milstein with Edelman

Claims 40-42 depend from independent claim 33.

As noted above, Milstein does not disclose or suggest complexing insulin with microparticles of a diketopiperazine derivative. Edelman does not make up for the deficiencies of Milstein. Edelstein merely broadly refers to "insulin regimes" or a "split -mixed" insulin regime. Neither Edelstein nor Milstein disclose complexing insulin with microparticles of a diketopiperazine derivative to deliver insulin monomers or dimers. Neither Edelstein nor Milstein contains a disclosure or suggestion of forming a complex. As shown by the attached Declaration, one cannot simply extrapolate from the co-precipitation-based encapsulation method disclosed in the prior art to derive a method that results in complexation between the insulin and the diketopiperazine derivative. Accordingly, claims 40-42 are not obvious over Milstein in view of Edelman.

Obviousness- type Double Patenting Rejections

Claims 33 and 35-39 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 4-7, and 10-14 of U.S. Patent No. 6,071,497 to Steiner *et al.* ("the '497 patent") and claims 1, 4-7, and 10-12 of U.S. Patent No. 6,428,771 to Steiner *et al.* ("the '771 patent"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Legal Standard

When determining whether the claims of an application define an invention that is an obvious variation of an invention defined in the claims of a patent, the claims of the application are compared with the claims in the patent, the disclosure in specification of the patent is not

considered in the analysis (*see* MPEP §§ 800-822). The MPEP explains that "[a] double patenting rejection of the obviousness-type is 'analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. § 103' except that the patent principally underlying the double patenting rejection is not considered prior art." MPEP § 804(II)(B)(1), citing *In re Braithwaite*, 379 F.2d 594, 154 U.S.P.Q. 29 (CCPA 1967). Therefore, analysis employed in an obviousness-type double patenting rejection parallels the guidelines for a 35 U.S.C. § 103 obviousness determination. *Id.*, citing *In re Braat*, 937 F.2d 589, 19 U.S.P.Q.2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985).

b. U.S. Patent No. 6,428,771 to Steiner et al. ("the '771 patent")

Claims 33 and 35-39 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 4-7, and 10-12 of the '771 patent.

This rejection is improper based on a comparison of pending claims 33 and 35-39 with claims 1, 4-7, and 10-12 of the '771 patent as shown below.

Claims as Amended	**Claims of the '771 Patent**
33. A method for delivering monomeric or dimeric insulin to a patient in need thereof, comprising administering to the patient a delivery formulation for the monomeric or dimeric insulin comprising an effective amount of insulin complexed with a diketopiperazine derivative, wherein the delivery formulation is prepared by complexing the insulin with	1. A microparticulate system for controlled drug delivery to the pulmonary system comprising: synthetic biodegradable polymeric microparticles incorporating therein a therapeutic, prophylactic or diagnostic agent, wherein the microparticles have a diameter between 0.5 microns and ten microns and are formulated to release the incorporated agent at

microparticles of the diketopiperazine derivative, wherein the diketopiperazine derivative has the formula 2,5-diketo-3,6-di(4-X-aminobutyl)piperazine, wherein X is selected from the group consisting of fumaryl, succinyl, maleyl, and glutaryl, and wherein the microparticles release monomeric or dimeric insulin upon dissociation. 35. The method of claim 33 wherein X is fumaryl. 36. The method of claim 33 wherein X is succinyl. 37. The method of claim 33 wherein X is maleyl. 38. The method of claim 33 wherein X is glutaryl. 39. The method of claim 33 wherein the composition is in a dry powder form administered to the lungs via inhalation.	a pH of 6.0 or greater under conditions present in the pulmonary system, in a pharmaceutically acceptable carrier for administration to the lungs, and wherein the microparticles are made from a material selected from the group consisting of diketopiperazines, poly(hydroxy acids), polyanhydrides, polyesters, polyamides, polycarbonates, polyalkylenes, polyvinyl compounds, polysiloxanes, polymers of acrylic and methacrylic acids, polyurethanes and co-polymers thereof, poly(butic acid), poly(valeric acid), poly(lactide-co-caprolactone), polysaccharides, copolymers and mixtures thereof. 4. The system of claim 1 wherein the agent is selected from the group consisting of proteins, polysaccharides, lipids, nucleic acids drugs, and combinations thereof. 5. The system of claim 4 wherein the agent is selected from the group consisting of insulin, calcitonin, felbamate, heparin, parathyroid hormone and fragments thereof, growth hormone, erythropoietin, AZT, DDI, G CSF, lamotrigine, chorionic gonadotropin releasing factor, luteinizing releasing hormone, vaccines,

	gene encoding adenosine deaminase, and Argatroban. 6. The system of claim 1 wherein the microparticles are a dry powder provided with an apparatus for administration of the microparticles to the lungs. 7. A method for controlled drug delivery to the pulmonary system comprising: administering to a patient in need of treatment an effective amount of synthetic biodegradable polymeric microparticles incorporating therein a therapeutic, prophylactic or diagnostic agent, wherein the microparticles have a diameter between 0.5 microns and ten microns and are formulated to release the incorporated agent at a pH of 6.0 or greater under conditions present in the pulmonary system, in a pharmaceutically acceptable carrier for administration to the lungs, and wherein the microparticles are made from a material selected from the group consisting of diketopiperazines, poly(hydroxy acids), polyanhydrides, polyesters, polyamides, polycarbonates, polyalkylenes, polyvinyl compounds, polysiloxanes, polymers of acrylic and methacrylic acids, polyurethanes and co-

	polymers thereof, poly(butic acid), poly(valeric acid), poly(lactide-co-caprolactone), polysaccharides, copolymers and mixtures thereof. 10. The method of claim 7 wherein the agent is selected from the group consisting of proteins, polysaccharides, lipids, nucleic acids drugs, and combinations thereof. 11. The method of claim 10 wherein the agent is selected from the group consisting of insulin, calcitonin, felbamate, heparin, parathyroid hormone and fragments thereof, growth hormone, erythropoietin, AZT, DDI, G CSF, lamotrigine, chorionic gonadotropin releasing factor, luteinizing releasing hormone, β-galactosidase and Argatroban. 12. The method of claim 7 wherein the microparticles are a dry powder provided with an apparatus for administration of the microparticles to the lungs.

Independent claims 1 and 7 of the '771 patent are directed to a microparticulate system for controlled drug delivery to the pulmonary system comprising synthetic biodegradable

polymeric microparticles incorporating therein a therapeutic, prophylactic or diagnostic agent and methods of using thereof. Claims 1, 4-7, and 10-12 of the '771 patent do not define a microparticle, wherein insulin is complexed with microparticles of a diketopiperazine derivative, nor do they define delivering monomeric or dimeric insulin to a patient, as required by independent claim 33, as amended. "Incorporating" as generally used in the art does not require a specific interaction between an agent and the particle in which it is incorporated. As shown by the attached Declaration, "complexing" describes particles with a specific type of interaction between the active agent and the diketopiperazine. Thus, "complexing" is not obvious in view of the mere use of the term "incorporating". Accordingly, claims 33 and 35-39 are not obvious over claims 1, 4-7, and 10-12 of the '771 patent.

c. U.S. Patent No. 6,071,497 to Steiner et al. ("the '497 patent")

Claims 33 and 35-39 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 4-7, and 10-14 of the '497 patent. This rejection is improper based on a comparison of pending claims 33 and 35-39 with claims 1, 4-7, and 10-14 of the '497 patent as shown below:

Claims as Amended	Claims of the '497 Patent
33. A method for delivering monomeric or dimeric insulin to a patient in need thereof, comprising administering to the patient a delivery formulation for the monomeric or dimeric insulin comprising an effective amount	1. A microparticulate system for drug delivery to the pulmonary system comprising: synthetic biodegradable microparticles which comprise a diketopiperazine and which have a diameter between 0.5 microns and ten microns

of insulin complexed with a diketopiperazine derivative, wherein the delivery formulation is prepared by complexing the insulin with microparticles of the diketopiperazine derivative, wherein the diketopiperazine derivative has the formula 2,5-diketo-3,6-di(4-X-aminobutyl)piperazine, wherein X is selected from the group consisting of fumaryl, succinyl, maleyl, and glutaryl, and wherein the microparticles release monomeric or dimeric insulin upon dissociation. 35. The method of claim 33 wherein X is fumaryl. 36. The method of claim 33 wherein X is succinyl. 37. The method of claim 33 wherein X is maleyl. 38. The method of claim 33 wherein X is glutaryl. 39. The method of claim 33 wherein the composition is in a dry powder form administered to the lungs via inhalation.	and which release an incorporated therapeutic, prophylactic, or diagnostic agent at a pH of 6.0 or greater, in a pharmaceutically acceptable carrier for administration to the lungs. 4. The system of claim 1 wherein the therapeutic, prophylactic or diagnostic agent is selected from the group consisting of proteins, polysaccharides, lipids, nucleic acids, other synthetic organic pharmaceutical compounds, and combinations thereof. 5. The system of claim 4 wherein the agent is selected from the group consisting of insulin, calcitonin, felbamate, heparin, parathyroid hormone and fragments thereof, growth hormone, erythropoietin, AZT, DDI, G CSF, lamotrigine, chorionic gonadotropin releasing factor, luteinizing releasing hormone, vaccines, gene encoding adenosine deaminase, and Argatroban. 6. The system of claim 1 wherein the microparticles are a dry powder provided with an apparatus for administration of the microparticles to the lungs.

	7. A method for delivery of particles to the pulmonary system comprising: administering to a patient in need of treatment an effective amount of synthetic biodegradable microparticles which comprise a diketopiperazine and which have a diameter between 0.5 microns and ten microns, in a pharmaceutically acceptable carrier for administration to the lungs. 10. The method of claim 7 wherein the microparticles further comprise a therapeutic, prophylactic, or diagnostic agent selected from the group consisting of proteins, polysaccharides, lipids, nucleic acids, other synthetic organic pharmaceutical compounds, and combinations thereof. 11. The method of claim 10 wherein the agent is selected from the group consisting of insulin, calcitonin, felbamate, heparin, parathyroid hormone and fragments thereof, growth hormone, erythropoietin, AZT, DDI, G CSF, lamotrigine, chorionic gonadotropin releasing factor, luteinizing releasing hormone, β.-galactosidase and Argatroban.

	12. The method of claim 7 wherein the microparticles are a dry powder provided with an apparatus for administration of the microparticles to the lungs. 13. The system of claim 1 wherein the therapeutic, prophylactic, or diagnostic agent is selected from the group consisting of vasoactive agents, neuroactive agents, hormones, anticoagulants, immunomodulating agents, cytotoxic agents, antibiotics, antivirals, antisense, antigens, and antibodies. 14. The method of claim 7 wherein the therapeutic, prophylactic, or diagnostic agent is selected from the group consisting of vasoactive agents, neuroactive agents, hormones, anticoagulants, immunomodulating agents, cytotoxic agents, antibiotics, antivirals, antisense, antigens, and antibodies.

Claims 1 and 7 of the '497 patent are directed to a microparticulate system for drug delivery to the pulmonary system comprising synthetic biodegradable microparticles which comprise a diketopiperazine, have a diameter between 0.5 microns and ten microns and release an incorporated therapeutic, prophylactic, or diagnostic agent and methods of using thereof.

Claims 1, 4-7, and 10-14 of the '497 patent do not define a microparticle, wherein insulin is complexed with microparticles of a diketopiperazine derivative, nor do they define delivering monomeric or dimeric insulin to a patient, as required by independent claim 33. As discussed above with respect to the claims of the '771 patent, the term "incorporate" as generally used in the art does not require a specific interaction between an agent and the particle in which it is incorporated. As shown by the attached Declaration, "complexing" describes particles with a specific type of interaction between the active agent and the diketopiperazine. Thus, "complexing" is not obvious in view of the mere use of the term "incorporating" in claim 1 of the '497 patent.

Claim 7 of the '497 patent, and its dependent claims, do not even specify that the diketopiperizine microparticles "incorporate" an active agent. Claim 7 merely requires administering an effective amount of synthetic biodegradable microparticles which comprise a diketopiperazine and have a diameter between 0.5 microns and ten microns, in a pharmaceutically acceptable carrier for administration to the lungs. Dependent claims, such as claim 8, specify that the microparticles further comprise a therapeutic, prophylactic, or diagnostic agent selected from a list of agents. "Comprise" is a standard term used in claims to indicate that a method or composition contains the listed subject matter and may contain additional, non-listed subject matter. Similar to the discussion above regarding the term "incorporate", the mere statement that microparticles "comprise" both a diketopiperazine and a particular agent, does not require a specific interaction between an agent and the microparticle.

Thus, "complexing" is not obvious in view of the mere use of the term "comprise". Additionally, claims 1, 4-7, and 10-14 of the '497 patent do not disclose delivering monomeric or dimeric insulin to a patient. Accordingly, claims 33, and 35-39 are not obvious over claims 1, 4-7, and 10-14 of the '497 patent.

Provisional Obviousness- type Double Patenting Rejections

Claims 33, 35-39 and 42 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 23-36 of copending U.S.S.N. 10/706,243 ("the '243 application") and claims 1-5, 8-10, 16-17, 23-24, 26-30, and 36 of copending U.S.S.N. 11/210,710 to Leone-Bay *et al.* ("the '710 application"). Claims 33, 35 and 40-42 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-5 and 17-23 of copending U.S.S.N. 11/329,686 to Boss *et al.* ("the '686 application"). Applicants respectfully traverse these rejections.

a. U.S.S.N. 10/706,243 to Steiner et al. ("the '243 application")

Claims 33, 35-39 and 42 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 23-36 of the '243 application. Applicants respectfully point out that the claims in the '243 application were amended on July 26, 2007. In this amendment, claims 28-30 and 33-35 were canceled and claims 23, 27 and 32 were amended. Additionally, new claims 37-54 were added.

Applicants believe that the new claims would not be used in an obviousness-type double patenting rejection. However, Applicants have included comments regarding the non-

obviousness of the pending claims in view of new claims 37-54 of the '243 application below to expedite allowance of this application.

This rejection is improper based on a comparison of pending claims 33, 35-39 and 42 with claims 23-27, 31, 32 and 36 of the '243 application as shown below.

Claims 33, 35-39 and 42 as Amended	**Claims 23-27, 31, 32 and 36, as pending, of the '243 Application**
33. A method for delivering monomeric or dimeric insulin to a patient in need thereof, comprising administering to the patient a delivery formulation for the monomeric or dimeric insulin comprising an effective amount of insulin complexed with a diketopiperazine derivative, wherein the delivery formulation is prepared by complexing the insulin with microparticles of the diketopiperazine derivative, wherein the diketopiperazine derivative has the formula 2,5-diketo-3,6-di(4-X-aminobutyl)piperazine, wherein X is selected from the group consisting of fumaryl, succinyl, maleyl, and glutaryl, and wherein the microparticles release monomeric or dimeric insulin upon dissociation.	23. A method for delivery of an active agent to the pulmonary system comprising: administering to a patient in need of treatment an effective amount of microparticles which comprise a diketopiperazine and the active agent and which have a diameter between 0.5 microns and ten microns, in a pharmaceutically acceptable carrier for administration to the lungs, wherein the carrier is air, wherein the microparticles are administered from a dry powder inhaler or from a container for a dry powder inhaler, and wherein the active agent is released from the microparticle at a pH of 6.0 or greater.
35. The method of claim 33 wherein X is fumaryl.	24. The method of claim 23, wherein the diketopiperazine has the formula 2, 5 -diketo-3,6-di(4-X-aminobutyl)piperazine, wherein X is selected from the group consisting of

	succinyl, glutaryl, maleyl, and furmaryl.
36. The method of claim 33 wherein X is succinyl.	25. The method of claim 24, wherein X is fumaryl.
37. The method of claim 33 wherein X is maleyl.	26. The method of claim 23, wherein the agent is a therapeutic agent selected from the group consisting of insulin, calcitonin, felbamate, heparin, parathyroid hormone and fragments thereof, growth hormone, erythropoietin, zidovudine (AZT), didanosine (DDI), granulocyte colony stimulating factor (G-CSF), lamotrigine, chorionic gonadotropin releasing factor, luteinizing releasing hormone, β-galactosidase, and Argatroban.
38. The method of claim 33 wherein X is glutaryl.	
39. The method of claim 33 wherein the composition is in a dry powder form administered to the lungs via inhalation.	
42. The method of claim 33 wherein the composition is provided in one or more unit doses of insulin, each dose equivalent to about 6 IU of insulin.	27. A microparticulate system for drug delivery to the pulmonary system comprising: microparticles incorporating therein a therapeutic, prophylactic or diagnostic agent, wherein the microparticles have a diameter between 0.5 microns and ten microns and are formulated to release the incorporated agent at a pH of 6.0 or greater, in a pharmaceutically acceptable carrier for administration to the lungs, wherein the carrier is air, wherein the microparticles are in a dry powder inhaler or a

	container for a dry powder inhaler, and wherein the microparticles consist essentially of the therapeutic, prophylactic or diagnostic agent and a material selected from the group consisting of poly(hydroxy acids), polyanhydrides, polyesters, polyamides, polycarbonates, polyalkylenes, polyvinyl compounds, polysiloxanes, polymers of acrylic and methacrylic acids, polyurethanes and co-polymers thereof, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), polysaccharides, and copolymers and mixtures thereof. Claims 28-30. (canceled) 31. The system of claim 27, wherein the agent is a therapeutic agent selected from the group consisting of insulin, calcitonin, felbamate, heparin, parathyroid hormone and fragments thereof, growth hormone, erythropoietin, zidovudine (AZT), didanosine (DDI), granulocyte colony stimulating factor (G-CSF), lamotrigine, chorionic gonadotropin releasing factor, luteinizing releasing hormone, β - galactosidase, and Argatroban.

	32. A method for drug delivery to the pulmonary system comprising: administering to a patient in need of treatment an effective amount of microparticles incorporating therein a therapeutic, prophylactic or diagnostic agent, wherein the microparticles have a diameter between 0.5 microns and ten microns and are formulated to release the incorporated agent at a pH of 6.0 or greater, in a pharmaceutically acceptable carrier for administration to the lungs, wherein the carrier is air, wherein the microparticles are administered from a dry powder inhaler or from a container for a dry powder inhaler, and wherein the microparticles consist essentially of the therapeutic, prophylactic or diagnostic agent and a material selected from the group consisting of poly(hydroxy acids), polyanhydrides, polyesters, polyamides, polycarbonates, polyalkylenes, polyvinyl compounds, polysiloxanes, polymers of acrylic and methacrylic acids, polyurethanes and co-polymers thereof, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), polysaccharides, and copolymers and mixtures thereof.

	Claims 33 - 35. (canceled) 36. The method of claim 32, wherein the agent is a therapeutic agent selected from the group consisting of insulin, calcitonin, felbamate, heparin, parathyroid hormone and fragments thereof, growth hormone, erythropoietin, zidovudine (AZT), didanosine (DDI), granulocyte colony stimulating factor (G-CSF), lamotrigine, chorionic gonadotropin releasing factor, luteinizing releasing hormone, β - galactosidase, and Argatroban.

Independent claims 23, 27 and 32 of the '243 application are directed to a method for delivery of an active agent to the pulmonary system (claim 23), a microparticulate system for drug delivery to the pulmonary system (claim 27) and a method for drug delivery to the pulmonary system (claim 32).

Claim 27 specifies that the microparticulate system comprises microparticles incorporating therein a therapeutic, prophylactic or diagnostic agent, wherein the microparticles have a diameter between 0.5 microns and 10 microns and are formulated to release the incorporated agent at a pH of 6.0 or greater, in a pharmaceutically acceptable carrier for administration to the lungs, wherein the carrier is air. Claim 27 also specifies that the microparticles consist essentially of the therapeutic, prophylactic or diagnostic agent and a

material selected from the group consisting of poly(hydroxy acids), polyanhydrides, polyesters, polyamides, polycarbonates, polyalkylenes, polyvinyl compounds, polysiloxanes, polymers of acrylic and methacrylic acids, polyurethanes and co-polymers thereof, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), polysaccharides, and copolymers and mixtures thereof. Further, claim 27 specifies that the microparticles are in a dry powder inhaler or a container for a dry powder inhaler.

Independent claim 32 specifies that the method comprises administering an effective amount of microparticles, and defines the microparticles in the same manner as claim 27. Further, claim 32 specifies that the microparticles are administered from a dry powder inhaler or a container for a dry powder inhaler.

Independent claims 27 and 32 of the '243 application, and their dependent claims, claims 31 and 36, specify that the material used to form the microparticles is from a list of materials that does not include diketopiperazines. Therefore claims 33, 35-39 and 42 are not obvious in view of claims 27, 31, 32, and 36 of the '243 application.

New claims 50 and 51 specify the same list of materials as independent claims 27 and 32. Similarly, new claims 37-39 and 52-54 depend directly or indirectly from claims 16 and 22 and specify that the material used to form the microparticles is from a different list of materials that does not include diketopiperazines. Therefore new claims 37-39 and 50-54 are not obvious in view of claims 27, 31, 32, and 36 of the '243 application.

Further, independent claims 27 and 32 of the '243 application, and their dependent claims, claims 31 and 36, do not define a microparticle, wherein insulin is complexed with microparticles of a diketopiperazine derivative, nor do they define delivering monomeric or dimeric insulin to a patient, as required by independent claim 33. As discussed above with respect to the claims of the '771 patent and the '497 patent, the term "incorporate" as generally used in the art does not require a specific interaction between an agent and the particle in which it is incorporated. As shown by the attached Declaration, "complexing" describes particles with a specific type of interaction between the active agent and the diketopiperazine. Thus, "complexing" is not obvious in view of the mere use of the term "incorporating" in claims 27 and 32 of the '243 application.

Additionally, new claims 37-39 and 52-54 depend directly or indirectly from independent claims 16 and 22. Independent claims 16 and 22 use the phrase "are formed of" to define the materials used to form the microparticles. This phrase is similar to the term "incorporating" discussed above. The phrase "are formed of" as generally used in the art does not require a specific interaction between an agent and the particle that it is used to form. As shown by the attached Declaration, "complexing" describes particles with a specific type of interaction between the active agent and the diketopiperazine. Thus, "complexing" is not obvious in view of the mere use of the phrase "are formed of" in new dependent claims 37-39 and 52-54 of the '243 application.

Independent claim 23 of the '243 application specifies that the method requires administering to a patient in need thereof microparticles which comprise a diketopiperazine and the active agent and have a diameter between 0.5 microns and ten microns, in a pharmaceutically acceptable carrier for administration to the lungs, wherein the carrier is air. Claim 23 and its dependent claims do not even specify that the diketopiperizine microparticles "incorporate" an active agent, rather these claims use the term "comprise". "Comprise" is a standard term used in claims to indicate that a method or composition contains the listed subject matter and may contain additional, non-listed subject matter. Similar to the discussion above regarding the term "incorporate", the mere statement that microparticles "comprise" both a diketopiperazine and an active agent, does not require a specific interaction between an agent and the microparticle. Thus, "complexing" is not obvious in view of the mere use of the term "comprise". Additionally, claims 23 and its dependent claims, claims 24-26, of the '243 application do not disclose delivering monomeric or dimeric insulin to a patient.

New claims 40-49 also use the term "comprise" to define the microparticles. As discussed above, the mere statement that microparticles "comprise" both a diketopiperazine and an active agent, does not require a specific interaction between an agent and the microparticle. Thus, "complexing" is not obvious in view of the mere use of the term "comprise". Additionally, new claims 40-49 of the '243 application do not disclose delivering monomeric or dimeric insulin to a patient.

New claims 50 and 51 use the term "consisting essentially of" to define the microparticles. The phrase "consisting essentially of" is a standard term used in claims to indicate that the microparticles contain the listed subject matter and may contain additional, non-listed subject matter if such additional materials "do not materially affect the basic and novel characteristic(s)" of the claimed invention. (M.P.E.P.§2111.03, citing *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976)). Similar to the discussion above regarding the term "comprise", the mere statement that microparticles "consist essentially of" both a specific listed material and an active agent, does not require a specific interaction between an agent and the microparticle. Thus, "complexing" is not obvious in view of the mere use of the term "consisting essentially of". Additionally, new claims 50 and 51 of the '243 application do not disclose delivering monomeric or dimeric insulin to a patient.

Accordingly for at least the reasons discussed above, claims 33, 35-39 and 42 are not obvious over claims 23-27, 31, 32 and 36 of the '243 application. Further, for at least the reasons discussed above, claims 33, 35-39 and 42 are not obvious over new claims 37-54 of the '243 application.

b. U.S.S.N. 11/210,710 to Leone-Bay et al. ("the '710 application") and U.S.S.N. 11/329,686 to Boss et al. ("the '686 application")

Claims 33, 35-39 and 42 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-5, 8-10, 16-17, 23-24, 26-30, and 36 of the '710 application. Claims 33, 35 and 40-42 were provisionally rejected under the judicially

created doctrine of obviousness-type double patenting over claims 1-5 and 17-23 of the '686 application.

Legal Standard

According to M.P.E.P. § 804 I(B)(1), "If a 'provisional' nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer."

Analysis

The present application was filed on November 21, 2003. The '710 application was filed on August 23, 2005. The '686 application was filed on January 10, 2006. Thus, the present application was filed prior to both the '710 application and the '686 application.

Applicants believe that all of the previous rejections to the present application have been overcome in view of the arguments provided herein and the Declaration submitted herewith. Applicants respectfully request withdrawal of the remaining provisional obviousness-type double patenting rejections over claims 1-5, 8-10, 16-17, 23-24, 26-30, and 36 of the '710 application and over claims 1-5 and 17-23 of the '686 application in accordance with M.P.E.P. § 804 I(B)(1). Applicants make this request solely to expedite allowance of the present application and reserve the right to traverse similar double patenting rejections, if such rejections are made, in the '710 application and/or '686 application.

Allowance of claims 33 and 35-42, as amended, is respectfully solicited.

Respectfully submitted,

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